Current perspectives

The role of anti-IgA antibodies in causing adverse reactions to gamma globulin infusion in immunodeficient patients: A comprehensive review of the literature

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Anaphylactic reactions to immunoglobulin infusions in immunodeficient patients with undetectable IgA have been attributed in several reports to IgG or IgE anti-IgA antibodies. However, other reports have not supported an association between such antibodies and the development of severe reactions. We have reviewed the articles reporting reactions to immunoglobulin products in IgA-deficient patients, as well as those describing the presence of such antibodies in the absence of reactions to infusions. A variety of factors might influence the association of adverse reactions with anti-IgA antibodies, including the serum concentration and isotype (IgG or IgE) of the anti-IgA antibody, its specificity (class or subclass specific), the method of measurement, and the IgA content of the gamma globulin infusion and its route of administration. The role of anti-IgA antibodies in causing anaphylaxis in IgA-deficient patients receiving gamma globulin therapy is still controversial. Larger (multicenter) studies are needed to further evaluate this association. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Anaphylaxis, anti-IgA antibody, IgA deficiency, immunoglobulin therapy*

There are 2 subclasses of IgA (IgA_1 and IgA_2) in human subjects. Furthermore, there are 2 allotypes of IgA_2 (IgA_{2m1} and IgA_{2m2}). The normal adult serum IgA level ranges between approximately 70 and 300 mg/dL. The clinical definition of IgA deficiency varies among reports and usually ranges between less than approximately 5 to 10 mg/dL.[1] However, approximately 25% of these subjects have levels of IgA that are measurable by using more sensitive methods; the remainder are completely lacking IgA.[2] In this review the term IgA deficiency refers to a level less than the detectable clinical range. This degree of IgA deficiency was found in 0.03% to 0.3% of healthy subjects (1:3,333 to 1:328) in the United States in 4 large prevalence studies including between 3,024 and 73,569 subjects each, although the definition of IgA deficiency was not consistent across all studies (range, 1-10 mg/dL).[2-6] A similar range of prevalence has been found in 8 additional reports from the United Kingdom, Scandinavia, and Australia.[3]

Abbreviations used

CVID: Common variable immunodeficiency
IGG2D: IgG_2 subclass deficiency
IRMA: Immunoradiometric assay
IVIG: Intravenous immunoglobulin
MIA: Membrane immunoassay
PHA: Passive hemagglutination
SCIG: Subcutaneous immunoglobulin
SIGAD: Selective IgA deficiency

Life-threatening reactions to administration of human IgG are rare in clinical practice.[7] In 1968, Vyas et al[8] reported the first anaphylactic reaction associated with intravenous infusion of a commercial gamma globulin product in a patient lacking serum IgA who had IgG anti-IgA antibodies. (In this review the term anaphylaxis is used for severe life-threatening systemic hypersensitivity reactions that might or might not be IgE mediated, as recommended in the Revised Nomenclature for Allergy for Global Use.[9]) Since that time, there have been several reports of anaphylactic reactions to immunoglobulin infusions in immunodeficient patients with undetectable IgA that were attributed to IgG or IgE anti-IgA antibodies.[10-13] However, other reports have not supported an association between such antibodies and the development of severe reactions.[14,15] Consequently, the significance of anti-IgA antibodies is still controversial. Nevertheless, as a result of these reports, virtually all gamma globulin products carry a warning advising caution when administering to IgA-deficient patients or even listing this condition as a contraindication for product administration. Anti-IgA antibodies that bind to all forms of IgA are designated class specific, and those that bind to 1 subclass or 1 allotype are designated limited specificity or subclass specific.[16,17] A variety of methods have been applied for measurement of anti-IgA antibodies. These include passive hemagglutination (PHA),[8] ELISA,[11] RIA,[18] immunoradiometric assay (IRMA),[19] particle gel immunoassay,[20] membrane immunoassay (MIA), and flow cytometry–based fluorescent bead immunoassays.[21]

A variety of factors might influence the association of adverse reactions with anti-IgA antibodies, including the serum concentration and isotype (IgG or IgE) of the anti-IgA antibody, its specificity (class or subclass specific), the method of measurement, the characteristics of the IgG product (IgA content), and the route of administration (intramuscular, intravenous, or subcutaneous).

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We have reviewed reports of reactions to gamma globulin products in IgA-deficient patients. We performed a PubMed search using combinations of key words, such as "IgA-deficient," "IgA deficiency," "anti-IgA antibody(ies)," "immunoglobulin infusion," "gamma globulin," "reaction," "anaphylaxis," and "anaphylactoid." We identified additional pertinent literature in the references of these reports. We reviewed all articles we found since 1968, when the first reaction was described by Vyas et al.[8] We have omitted reports that focus exclusively on reactions to other blood products.

IgG ANTI-IgA ANTIBODIES IN HEALTHY SUBJECTS

Among studies evaluating between 19 and 358 IgA-deficient subjects each, class-specific IgG anti-IgA was detected in 24% to 32%. Class-specific IgG anti-IgA was not found in 333 subjects with detectable IgA.[2,6] However, in one other report class-specific anti-IgA was present in 17% of 58 IgA-deficient blood donors, in 3 (2%) of 142 non–IgA-deficient (pregnant and nonpregnant) women, and in 1 (0.5%) of 200 non–IgA-deficient blood donors.[22] Note that in this report a titer as low as 1:4 determined by using the PHA method was considered positive.

Subclass-specific IgG anti-IgA antibodies have been found in 5% to 7% of IgA-deficient blood donors,[3,16,22] as well as 6% of non–IgA-deficient subjects.[22] Rivat et al[23] found subclass-specific IgG anti-IgA by means of PHA in as many as 59% of 1010 blood donors. The reason for such a high frequency is unclear, but the authors speculated it could be because they included PHA titers of less than 1:8.

IgG ANTI-IgA ANTIBODIES ASSOCIATED WITH ADVERSE REACTIONS TO GAMMA GLOBULIN PRODUCTS

Three studies including a total of 325 immunodeficient (common variable immunodeficiency [CVID], IgG_2 subclass deficiency (IGG2D), and selective IgA deficiency [SIGAD]) patients lacking IgA found 99 (30%) patients with IgG anti-IgA antibodies.[18,24,25] For most of these, the specificity of the anti-IgA was not determined; only 7 were stated to have class-specific IgG anti-IgA, and no patient with IgA levels of greater than 5 mg/dL had anti-IgA antibodies.[18] The great majority of those who received immunoglobulin therapy tolerated their infusions (a precise number or fraction could not be determined from the data in the report).

After Vyas et al[8] reported the first IgA-deficient patient with class-specific IgG anti-IgA and anaphylaxis to intramuscular immunoglobulin, several reports described similar patients with moderate symptoms (eg, abdominal pain, myalgia, nausea, fevers, and/or rigors) or anaphylaxis to gamma globulin infusions in the presence of IgG anti-IgA antibodies, which were detected by using different methods. We found reports of 27 patients with such presentations, the characteristics of whom are listed in Table I.[8,10-13,20,24-33] Some of these reports lacked information about the type of anti-IgA antibodies (class or subclass specific), patient diagnosis, or total IgA level.

Apart from 1 patient whose IgA level was not stated, all patients had IgA levels of less than 10 mg/dL. When the specificity of the IgG anti-IgA was reported (10 of the 27 cases), all antibodies were class specific. Twenty-four (89%) of 27 patients were given a diagnosis of CVID, whereas only 2 had SIGAD and 1 had IGG2D. There was no sex predilection in the development of these reactions. Interestingly, apart from 1 pediatric patient (age 15 years), all other patients with age reported were adults. It is impossible to gauge accurately the age composition of the patient populations represented in these reports, although it appears that there is a great preponderance of adults. The IgA content for all reported immunoglobulin infusions ranged from 0.4 to 2500 μg/mL.

There were 23 (85%) patients who had anaphylaxis, whereas 4 others had only moderate reactions. All episodes were secondary to intravenous or intramuscular administration. When the IgA content of the formulation was reported, most patients had reactions to an intravenous immunoglobulin (IVIG) product with IgA levels of 50 μg/mL or greater. Ten of these patients (including those with very high IgG anti-IgA titers) tolerated IVIG infusion with much lower IgA content, and 1 tolerated the same product after treating it with autologous plasma (patient 17). One other patient (patient 6) was premedicated with a corticosteroid and antihistamine and tolerated an IVIG formulation with mildly higher IgA content. In addition, 3 of the above patients, as well 1 other patient (patient 16) tolerated IVIG with high IgA content (≤2.5 mg/mL) when their anti-IgA titers became undetectable after initial therapy with low-IgA IVIG or after IVIG pretreatment with autologous plasma. In addition, 8 of these 27 patients tolerated subcutaneous immunoglobulin (SCIG). Six did not receive further gamma globulin therapy. The ability to tolerate SCIG was thought to be due to gradual exposure to IgA absorbed slowly from the subcutaneous compartment.[13]

Given that IgG anti-IgA antibodies are found in roughly one third of patients who are IgA deficient, their role in triggering anaphylaxis with gamma globulin infusion is not firmly established. Some reports described complement consumption during anaphylaxis to IVIG in patients with class-specific IgG anti-IgA,[10,26] whereas another did not.[27] In addition, low-level complement activation has been observed after infusions of IVIG with 2.9 μg/mL IgA or less without reactions in patients with or without class-specific IgG anti-IgA.[28]

Nadorp et al[18] conducted a unique study in which they administered purified radiolabeled IgA to IgA-deficient patients (IgA level, <2 mg/dL) with IgG anti-IgA antibodies. They described 1 patient with class-specific IgG anti-IgA measured by means of RIA who had an anaphylactic reaction after intravenous injection of less than 1 mg of purified iodine 131–labeled IgA. One other patient with IgG anti-IgA had fever and vomiting after radiolabeled IgA infusion. They described 5 additional patients with class-specific and 1 with subclass-specific IgG anti-IgA, all of whom tolerated intravenous infusions of purified radiolabeled IgA. The occurrence of symptoms was directly related to higher concentrations of anti-IgA. These IgG anti-IgA antibodies could fix complement *in vitro*, but this was not studied *in vivo*. These authors also showed that patients with IgG anti-IgA demonstrated increased catabolism of IgA *in vivo*.

Ferreira et al[15] reported 2 patients with Wiskott-Aldrich syndrome with high titers of subclass-specific IgG anti-IgA_1 who also had increased endogenous serum IgA levels (288 and 436 mg/dL). One had anaphylaxis, and 1 had a moderate reaction.

In summary, most reported adverse events occur in patients with very low IgA levels and high-titer class-specific anti-IgA receiving gamma globulin products containing relatively high concentrations of IgA. There might be a threshold phenomenon

TABLE I. Characteristics of IgA-deficient patients with IgG anti-IgA antibodies reacting to gamma globulin products

Patient no.	Age (y)	Sex	Diagnosis	IgA (mg/dL)	IgG anti-IgA titer	Method	Specificity	Reaction	Product causing reaction/IgA content*	Product tolerated/IgA content*	Reference
1	UK	M	CVID	<5	1:262,144	PHA	UK	ANA	IVIG/<20		24
2	44	F	CVID	<1	1:32,718	ELISA	Class	MOD	IVIG/720	IVIG/20	10
3	22	F	CVID	1.2	1:12,800†	ELISA	Class	ANA	IVIG		25
4	41	M	CVID	0	1:2,560-10,240	PHA	Class	ANA	IVIG/500	IVIG/3-23	26
5	15	M	CVID	0	1:8,000†	PHA	UK	ANA	IVIG/15	IVIG/1.6	11
6	28	M	CVID	<0.09	1:6,400	ELISA	UK	ANA	IVIG (<100)	IVIG/160‡	12
7	33	F	CVID	<0.09	1:6,400	ELISA	UK	ANA	IVIG/<100	SCIG	12
8	33	F	CVID	<0.09	1:1,600	ELISA	UK	ANA	IVIG/2,500	SCIG	12
9	45	F	CVID	<10	1:1,000	PHA	Class	ANA	IVIG/270		27
10	39	M	IGG2D	<1	1:500	ELISA	Class	ANA	IVIG/270	IVIG (0.4-2.9)	28
11	49	F	CVID	7	1:500	ELISA	Class	MOD	IVIG/720	IVIG (0.4-2.9)	28
12	49	F	CVID	<0.09	1:400	ELISA	UK	ANA	IVIG <100	SCIG	12
13	36	F	CVID	<0.09	1:400	ELISA	UK	MOD	IVIG/(50-6,000)	SCIG	12
14	30	F	SIGAD	<0.05	1:256	PGI	UK	ANA	RhoGAM		20
15	20	F	CVID	<1	1:200	ELISA	Class	ANA	IVIG/270-720	IVIG (0.4-2.9)	28
16	52	F	CVID	<5-10	1:64	PGI	UK	ANA	IVIG	IVIG (50-2,500)§	30
17	40	M	CVID	<6.7	1:32	PGI	UK	ANA	IVIG/100	IVIG (100-2,500)¶	30, 31
18	33	F	CVID	<5	1:4	PGI	UK	ANA	IVIG/(2,000-2,500)	IVIG (<50)	30
19	62	F	CVID	<5	1:4	PGI	UK	ANA	IVIG (15-2,500)	IVIG (50-2,500)¶	30
20	70	M	CVID	<5	1:2	PGI	UK	ANA	IVIG (<2,000)	IVIG (<50-2,500)¶	30
21	19	F	CVID	<0.001	3.95 μg/mL	ELISA	Class	ANA	IVIG <10	SCIG	29
22	18	F	SIGAD	0	Yes‖	PHA	Class	ANA	IMIG		8
23	UK	M	UK	UK	Yes	PHA	Class	ANA	IMIG or IVIG		32
24	UK	M	CVID	<0.1	Yes	PHA	UK	ANA	IMIG	SCIG	13
25	UK	M	CVID	<0.1	Yes	PHA	UK	ANA	IMIG	SCIG	13
26	UK	F	CVID	<0.1	Yes	PHA	UK	ANA	IVIG/1,140	SCIG	13
27	29	F	CVID	<5	Yes	UK	UK	MOD	IVIG	IVIG	33

ANA, Anaphylaxis; *F*, female; *IMIG*, intramuscular immunoglobulin; *M*, male; *MOD*, moderate systemic symptoms, including abdominal pain, myalgia, nausea, fever, and rigors; *PGI*, particle gel immunoassay; *UK*, unknown.
*Expressed as micrograms per milliliter.
†Patient with IgE anti-IgA.
‡Premedicated with steroids and antihistamine.
§IVIG was well tolerated when anti-IgA titer was no more detectable.
¶IVIG with increased IgA content was well tolerated when anti-IgA titer was no more detectable.
‖Yes indicates anti-IgA is present, titer not specified.

for symptoms associated with IgG anti-IgA because patients reported to react tend to have higher levels. However, it is difficult to compare values across studies because of different methods of measurement. Furthermore, some of these patients were reported to have IgE anti-IgA antibodies, which might also be pathogenic and have been less frequently studied (see below). In addition, there are examples of patients with anti-IgA who tolerate many exposures to IgA-containing blood products (also see the next section) or even infusion of purified IgA.

IgG ANTI-IgA ANTIBODIES NOT ASSOCIATED WITH ADVERSE REACTIONS

The literature cited above contained some patients with anti-IgA antibodies who reacted to gamma globulin but more who did not. A few studies have focused on patients with anti-IgA who tolerated gamma globulin.[14,17,25,34,35] We have found reports of a total of 49 IgA-deficient patients with IgG anti-IgA who tolerated gamma globulin. The IgA level was less than 7 mg/dL in 37 (76%) of the patients; the level was not stated for 12 others. The characteristics of these patients are summarized in Table II.* Some reports also omitted details, such as age, sex, and the specificity and titer of IgG anti-IgA. More than 70% of patients had CVID, and the others had diagnoses including unspecified hypogammaglobulinemia, SIGAD, IGG2D, and unspecified "primary immunodeficiency." There were no patients noted in the pediatric age group; however, age was not stated for two thirds of these patients. Sixty-five percent of these patients tolerated IVIG, intramuscular immunoglobulin, or both, and the others only received SCIG. The IgA content for most infusions was not stated, but many patients were reported to tolerate IVIG with an increased IgA concentration (≥500 μg/mL). IgG anti-IgA specificity was only reported in 18% of these patients (6 subclass and 3 class specific).

IGE ANTIBODIES TO IGA

A few studies have reported adverse reactions to blood products associated with anti-IgA antibodies of the IgE class.

*References 12–14, 17, 20, 24, 25, 29, 32, 35, and 36.

TABLE II. Characteristics of IgA-deficient patients with IgG anti-IgA antibodies tolerating gamma globulin products

Patient no.	Age (y)	Sex	Diagnosis	IgA (mg/dL)	IgG anti-IgA titer	Method	Specificity	Product tolerated/IgA content*	Reference
1	49	F	CVID	<7	1:524,000	PHA	UK	IVIG/18	36
2	UK	F	CVID	UK	1:3,200	ELISA	UK	IVIG/540	17
3	46	F	Hypogam	<0.001	1:2,000	PHA	Class	IMIG	14
4	40	M	CVID	<0.09	1:800	ELISA	UK	IVIG/SCIG	12
5	UK	M	CVID	UK	1:640	ELISA	UK	IVIG/540	17
6	UK	M	CVID	UK	1:320	ELISA	UK	IVIG/540	17
7	44	M	CVID	<0.09	1:200	ELISA	UK	IVIG	12
8	UK	UK	CVID	1.6	1:200	ELISA	Class	IVIG/IMIG	25
9	31	M	CVID	<0.09	1:100	ELISA	UK	IVIG/SCIG	12
10	UK	M	CVID	UK	1:80	ELISA	UK	IVIG/540	17
11	UK	M	CVID	UK	1:50	ELISA	UK	IVIG/540	17
12	UK	UK	CVID	1.6	1:50	ELISA	Limited	IVIG	25
13	50	F	SIGAD	<0.05	1:32	PGI	UK	IVIG/100-500	20
14	53	F	SIGAD	<0.05	1:32	PGI	UK	IVIG/100-500	20
15	UK	UK	PID	UK	1:8-256	PHA	Limited	IMIG or IVIG	32
16	UK	UK	PID	UK	1:8-256	PHA	Limited	IMIG or IVIG	32
17	UK	UK	PID	UK	1:8-256	PHA	Limited	IMIG or IVIG	32
18	UK	UK	PID	UK	1:8-256	PHA	Limited	IMIG or IVIG	32
19	42	M	CVID	UK	1:8	PGI	UK	IVIG/100-500	20
20	UK	UK	CVID	UK	1:4	PGI	UK	IVIG/100-500	20
21	55	F	CVID	UK	1:2	PGI	UK	IVIG/100-500	20
22	60	F	CVID	0.002	3.98 μg/mL	ELISA	Class	SCIG	29
23	60	M	CVID	0.003	0.461 μg/mL	ELISA	Limited	SGIG	29
24	UK	M	Hypogam	<5	3+†	ELISA	UK	SCIG	35
25	UK	M	Hypogam	<5	3+	ELISA	UK	SCIG	35
26	UK	F	Hypogam	<5	3+	ELISA	UK	SCIG	35
27	UK	M	SIGAD	<5	3+	ELISA	UK	SCIG	35
28	UK	M	CVID	<0.1	Yes‡	PHA	UK	IVIG	13
29	UK	M	CVID	<0.1	Yes	PHA	UK	IVIG	13
30	UK	F	CVID	<0.1	Yes	PHA	UK	IVIG	13
31	UK	F	CVID	<0.1	Yes	PHA	UK	IVIG	13
32	UK	UK	CVID	<5	Yes	PHA	UK	IVIG/<20	24
33	UK	UK	CVID	<5	Yes	PHA	UK	IVIG/<20	24
34	UK	UK	CVID	<5	Yes	PHA	UK	IVIG/<20	24
35	UK	UK	CVID	<5	Yes	PHA	UK	IVIG/<20	24
36	UK	UK	CVID	<5	Yes	PHA	UK	IVIG/<20	24
37	UK	UK	CVID	<5	Yes	PHA	UK	IVIG/<20	24
38	UK	UK	IGG2D	<5	Yes	PHA	UK	IVIG/<20	24
39	UK	F	CVID	<0.1	Yes	PHA	UK	SCIG	13
40	UK	M	CVID	<0.1	Yes	PHA	UK	SCIG	13
41	UK	UK	CVID	<5	Yes	ELISA	UK	SCIG	35
42	UK	UK	CVID	<5	Yes	ELISA	UK	SCIG	35
43	UK	UK	CVID	<5	Yes	ELISA	UK	SCIG	35
44	UK	UK	CVID	<5	Yes	ELISA	UK	SCIG	35
45	UK	UK	CVID	<5	Yes	ELISA	UK	SCIG	35
46	UK	UK	CVID	<5	Yes	ELISA	UK	SCIG	35
47	UK	UK	CVID	<5	Yes	ELISA	UK	SCIG	35
48	UK	UK	CVID	<5	Yes	ELISA	UK	SCIG	35
49	UK	UK	SIGAD	<5	Yes	ELISA	UK	SCIG	35

F, Female; *Hypogam*, hypogammaglobulinemia; *IMIG*, intramuscular immunoglobulin; *M*, male; *PGI*, particle gel immunoassay; *PID*, primary immunodeficiency; *UK*, unknown (in the column "IgA level," UK indicates that the actual IgA level was not stated clearly in the report).

*Expressed as micrograms per millimeter.

†Indicates that the titer was read as strongly positive on a semiquantitative scale.

‡Yes indicates anti-IgA present, titer not specified.

Burks et al[11] reported 2 patients with CVID and undetectable IgA with IgE anti-IgA (specificity unknown). One had anaphylaxis with IVIG and 1 with IgA-deficient plasma. They subsequently tolerated IVIG products with a lower content of IgA. Both patients also had high-titer IgG anti-IgA (specificity unknown). IgE anti-IgA was not detected in 20 healthy control subjects, in 10 patients with CVID without adverse reactions to IVIG, and in 10 atopic patients with increased serum IgE levels. In 1 of these patients, the presence of IgE anti-IgA was not replicated in another study using a similar ELISA method.[24]

Ferreira et al[25] found subclass-specific IgE anti-IgA_1 by means of ELISA in 1 patient with CVID having high-titer class-specific

IgG anti-IgA. This patient had anaphylaxis with IVIG, which was discontinued, and further therapy was refused. Both IgG and IgE anti-IgA antibodies disappeared after cessation of therapy. In a follow-up study these authors reported a patient with hyper-IgM syndrome, a diagnosis that is generally not compatible with an ability to produce specific IgE, who was not found to have IgG anti-IgA but had subclass-specific IgE anti-IgA_1. This patient tolerated IVIG.[15]

Limaye et al[36] reported a patient with CVID with IgA levels of less than 7 mg/dL and an increased IgG anti-IgA titer who had a history of 2 anaphylactic reactions to blood products. Before IVIG therapy, she underwent skin testing with 2 different IVIG concentrations. They did not measure IgE anti-IgA levels but did report a positive skin test result ("inflammation at 30 minutes") with an IVIG product containing between 61 and 540 μg/mL IgA and a negative skin prick test result with an IVIG product with a lower IgA content (18 μg/mL). The patient tolerated treatment with the latter.

Bjorkander et al[24] found IgG anti-IgA in 74 immunodeficient patients with IgA levels of less than 5 mg/dL, 8 of whom were receiving IVIG (IgA level, <20 μg/mL). One of these patients had anaphylaxis, whereas the other patients tolerated their IVIG infusions. None had IgE anti-IgA,[24] including 1 patient who was reported to be IgE anti-IgA positive by Burks et al.[11] The discrepancy could not be resolved because both ELISA systems had comparable sensitivity (1 ng/mL). De Albuquerque Campos et al[17] found IgG anti-IgA in 5 of 20 patients with CVID, 18 of whom received gamma globulin; none of these had IgE anti-IgA by means of ELISA. Homburger et al[19] did not find any patients with IgE anti-IgA among 20 with IgG class-specific or subclass-specific anti-IgA. Nadorp et al[18] also did not detect IgE anti-IgA by means of radioimmunoelectrophoresis and documented negative skin test results with purified IgA in 7 patients with IgG anti-IgA, including 1 with class-specific IgG anti-IgA who had anaphylaxis with intravenous injection of purified IgA (see above). The patients in the last 2 studies were not reported to receive immunoglobulin therapy.

We have evaluated 22 immunodeficient patients with IgA levels of less than 5 mg/dL receiving immunoglobulin therapy. One patient (patient 17, Table I) had class-specific IgG anti-IgA antibodies and a history of anaphylaxis to IVIG. One other patient had class-specific IgG anti-IgA, and a third had subclass-specific IgG anti-IgA_2 (patients 22 and 23, Table II). Both of these patients only received SCIG, which was well tolerated. None of the 22 patients evaluated had IgE anti-IgA antibodies by means of ImmunoCAP or ELISA.[29]

Thus IgE anti-IgA has been less frequently studied than IgG anti-IgA. When both have been studied together, anti-IgA of the IgE class occurs much less frequently than IgG. As detailed at the beginning of this section, we found 4 patients described in the literature who were reported to have IgE anti-IgA antibodies.[11,15,25] Three of them have had anaphylactic reactions to gamma globulin or another blood product and also had IgG anti-IgA. It is therefore unclear which antibody (if either) is responsible for the reactions in these patients.

IgG SUBCLASSES OF ANTI-IgA ANTIBODIES

Bjorkander et al[24] measured IgG subclasses of anti-IgA antibodies in 74 immunodeficient patients with IgA levels of less than 5 mg/dL. All had IgG_1 anti-IgA, and IgG_2 anti-IgA occurred in 26%, IgG_3 occurred in 15%, and IgG_4 occurred in 30%. Du Albuquerque Campos et al[17] measured subclasses of IgG anti-IgA in 5 patients. Similarly, all had IgG_1, 2 also had IgG_2 and IgG_4, and 1 also had IgG_2, IgG_3, and IgG_4. Only 1 patient had an anaphylactic reaction to IVIG, and no correlation with IgG subclass of anti-IgA was noted. Similarly, Hammarstrom et al[37] measured IgG subclasses of anti-IgA antibodies in 7 patients; all had IgG_1, and some had varying amounts of other subclasses of IgG ($IgG_2 > IgG_4 > IgG_3$).

OTHER CLASSES OF ANTI-IgA ANTIBODIES

Very few studies have looked for classes of anti-IgA antibodies other than IgG or IgE. In patients with absent serum IgA and having IgG anti-IgA, Bjorkander et al[24] also found IgM anti-IgA in 15% and IgD anti-IgA in 9%. There was no clinical correlation with these classes of anti-IgA, and no patient who did not make IgG anti-IgA produced an anti-IgA of another class. Ferreira et al[25] reported a single patient among 106 healthy blood donors with subclass-specific IgM anti-IgA_1 who did not have IgG anti-IgA.

VARIABILITY OVER TIME

Several studies have observed increasing titers of IgG (or IgE) anti-IgA before an anaphylactic reaction.[10,11,24,26] Furthermore, some studies found decreasing levels of IgG anti-IgA after continued therapy either with IVIG or SCIG.[10,11,26,30,35,36]

Sundin et al[35] followed 40 patients with IgA deficiency and IgG anti-IgA for an average of 14 years. Anti-IgA persisted in 36 and disappeared in 4 patients. Thirteen patients (2 with IgA deficiency and 11 with CVID) were treated with SCIG. For 7 of these patients, SCIG contained up to 5 mg/mL IgA, whereas for the other 6 patients, SCIG contained less than 80 μg/mL IgA. The anti-IgA disappeared in patients receiving SCIG with high IgA content, whereas it persisted in those who received the low IgA product. We found 1 patient with CVID and class-specific IgG anti-IgA that doubled during a 6-month observation period while being treated without adverse reactions with SCIG.[29]

COMPARISON OF DIFFERENT METHODS FOR MEASURING IgG ANTI-IgA ANTIBODIES

Several studies have compared different methods of measuring IgG anti-IgA antibodies in the same groups of patients.[11,19,35,38] The methods compared included PHA, ELISA, IRMA, MIA, and flow cytometric platform solid immunoassays. Some consider the ELISA and MIA methods slightly more sensitive than PHA.[38] We have found good correlation between ELISA, PHA, and a fluorescent bead method.[29] For measurement of IgG anti-IgA levels, the PHA, IRMA, and fluorescent bead methods are available commercially from reference laboratories.

Mainly ELISA methods have been used to measure IgE anti-IgA. ImmunoCap has also been used in our study[29]; no IgE anti-IgA was found in 3 patients with IgG anti-IgA, one of whom had anaphylaxis with IVIG.

CONCLUSION

The role of IgG or IgE anti-IgA antibodies in anaphylaxis in IgA-deficient patients receiving gamma globulin therapy remains controversial. Anaphylaxis has been reported in IgA-deficient

patients when these antibodies were not detected,[13] and many patients with these antibodies can tolerate gamma globulin infusion.

Nevertheless, it is possible that IgG anti-IgA antibodies could have a role in very rare anaphylactic reactions to IgG therapy. There might be a threshold phenomenon because among cases reported in the literature, most appear to be associated with the highest levels measured. There might also be a role for the amount of IgA in the infused IgG because some who reacted tolerated infusions with products containing less IgA. It is possible that low-IgA-content products do not lead to a sufficient concentration of IgG-IgA immune complexes to provoke a reaction in the recipient. However, it is also possible that some other characteristic of low-IgA-content products causes them to be better tolerated. Most reported cases of anaphylaxis with anti-IgA appear to occur in adults, and there might be a role of prolonged exposure over time, leading to increased levels that eventually precipitate a reaction. Class-specific antibodies are found in the majority of reacting patients, and all reported IgA-deficient patients with IgG anti-IgA of limited specificity tolerate their infusions. Of note, we have not found reports of fatal anaphylaxis from gamma globulin infusion, regardless of IgA status. Subcutaneous infusions appear to be tolerated by patients with anti-IgA antibodies. We found no reports of anaphylactic reactions to SCIG in IgA-deficient patients, and several patients with IgG anti-IgA antibodies have been found to tolerate SCIG without any adverse effects. Larger multicenter studies are needed to evaluate the role of these antibodies and their association with the rare anaphylactic reactions to gamma globulin. Animal models might be helpful in providing a proof of principle and identifying possible mechanisms.

IgG therapy should never be withheld from an IgA-deficient patient solely because of concern for the theoretic risk of a rare serious adverse reaction. There are insufficient data to warrant a general recommendation for screening for anti-IgA antibodies in these patients. The predictive value of a positive result of any level is not established, although there might be increased risk at higher levels. In any patient, regardless of IgA level, who is having significant systemic symptoms with IVIG, switching to SCIG should be considered. If an IgA-deficient patient is reacting to IVIG and SCIG is not an option (eg, the patient requires high anti-inflammatory doses of IVIG), use of a low-IgA-content product should be considered. The presence of a high level of IgG anti-IgA antibodies could support such a choice.

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